Lyme Disease and the Treatment Guidelines of the Infectious Disease Society of America.

DW Richardson MD FRCP(C), Kingston, Ontario.

In 2006 the Infectious Diseases Society of America published guidelines for the assessment, treatment, and prevention of Lyme disease (1). These guidelines appear to be researched and thought out. They also have distinct limitations. This paper is an attempt to review the guidelines, as they pertain to Lyme disease, from a critical point with the goal of evaluating them from a perspective that may have been missed by the Committee.

To put the issue into perspective, it is no secret that there is taking place in America today a debate regarding the long-term use of antibiotics in the treatment of Lyme disease. One group, and I believe the Infectious Diseases Society of America committee expresses this point of view, believes antibiotics should be given for only a two to four week period in the treatment of Lyme disease, whether it be in the early, middle, or late phase of the disease. Another group, including various American and European authors, feels that patients with Lyme disease, in the more advanced form, require treatment over a much longer period of time in order to eradicate an infection that they believe to be extremely difficult to eradicate. This paper will examine the guidelines of the committee and its supporting literature from what I hope will be a reasonably open approach to this debate.

The Issue of Prophylaxis for a Tick Bite:

Patients in areas endemic for Lyme disease may present with a history of a recent tick bite (within 72 hours of the bite), and the question is whether these patients should receive prophylactic antibiotic therapy. The Committee has issued the following guidelines on this issue:

"For prevention of Lyme disease after a recognized tick bite, routine use of antimicrobial prophlylaxis or serologic testing is not recommended. A single dose of doxycycline (4mg/kgm up to 200 mg) may be offered to adults and to children over 8 yrs of age under the following conditions:

1. The attached tick can readily be identified as an I. scapularis tick to have been attached for greater than 36 hours.
2. Prophylaxis is started within 72 hours.
3. Ecologic information indicates that the local rate of infection of these ticks with B. Burgdorferi is greater than 20%.
4. Doxycycline is not contraindicated as in pregnancy or children under eight years of age."

This guideline appears to ignore an article by Nadelman (14) that appeared in the New England Journal of Medicine in July 12, 2001. In a study, geographically set in an area of New York State endemic for Lyme disease, 482 patients who had removed an I-scapularis tick, and who received medical attention within 72 hours, were treated with either a single oral dose of 200 mg of doxycycline or placebo.

Results showed that only one of 235 patients receiving doxycycline developed erythema migrans, while 8 of 247 patients in the placebo group developed this lesion.

The difference is significant at the p<.04 level. This paper offers scientific evidence that supports single dose prophylaxis with doxycycline in contrast to the guidelines of the committee which state that in certain situations a prophylactic dose of doxycycline may be offered to a patient. One could argue that an infection rate of 3.2% in the placebo group is not a large percentage, but when one considers the stress, anxiety, and longer antibiotic regimen required to treat the target lesion of erythema migrans, prophylaxis does appear indicated.

Moreover the statement that "the excellent efficacy of antibiotic treatment of Lyme disease if infection were to develop" also needs to be put into perspective. Whereas it is true that patients with early disseminated erythema migrans have a high rate of treatment cures, a small but significant percentage of patients do not have a successful treatment outcome.

In a paper by Dattwyler et al (2) comparing the efficacy of ceftriaxone with doxycycline in a group of 133 patients with disseminated Lyme disease without meningitis, the cure rate was 85% with ceftriaxone and 88% with doxycycline. There was however a significant group of patients that reported residual symptoms at follow-up, 27% in the ceftriaxone group and 14% in the doxycycline group for a total of 20%. An important point in the Dattwyler paper is the inadequacy of the ELISA serology test for Lyme disease. Only 71% of these patients with the classic cutaneous manifestation of Lyme Disease tested positive on the ELISA test, suggesting the test can have a failure rate of around 30%.

The author is clearly concerned about the persistence of residual symptoms in patients in his study:

"The clinical significance of the persistent symptoms is difficult to assess. Early studies of Lyme disease focussed primarily on the most severe outcomes of the disease, and in the past patients with minor symptoms have generally been considered to have a favourable outcome. Although there are several possible explanations for the presence of residual symptoms—including continued infection, an immunologic process, permanent tissue damage resulting from the initial infection, and co-infection with another tick-borne pathogen—the cause of post-treatment symptoms remains to be addressed in future studies.

Signs and symptoms attributable to the nervous or musculoskeletal system have been noted by other investigators. Two separate large retrospective studies of patients treated for early Lyme disease found a surprisingly high incidence of continued signs and symptoms, especially if treatment were delayed. Shadick et al. (3) found that 34% of patients in a suburban area of highly endemic disease just north of Boston who had been treated for early Lyme disease had long-term sequelae including arthritis, arthralgia, cognitive impairment and neuropathy. A similar study in Westchester County, New York, found that 114 of the 215 patients studied (53%) had persistent signs and symptoms, including neurologic, cardiac, and musculoskeletal." (4)

Thus it appears from different studies of early Lyme disease that there is a rate of mild to severe persistent symptoms that continues after treatment, and that fatigue and musculoskeletal symptoms are the most common. If patients are treated early this rate may be about 10%, but if treatment is delayed the rate rises to 30% or higher, as in the study by Shadick and Asch.

Table 1. provides a summary of studies that show persistent symptoms after recommended treatment following IDSA Guidelines.

STUDIES SHOWING PATIENTS WITH PERSISTENT SYMPTOMS AFTER RECOMMENDED TREATMENT ACCORDING TO THE IDSA GUIDELINES.

Stage of Disease	% of Patients with ongoing **s**ymptoms	Principal author.
Early disseminated disease without meningitis	12-15%	Dattwyler RJ, NEJM:337 (31), 289-294 (1997)
Early disseminated disease treated early	5%	Nadelman RB Am J Med: 88, 21-6 (1990)
Early Lyme disease some delay in treatment	34%	Shadick NA Ann. Int. Med: 121, 560-7 (1994)
Early Lyme dis. some delay in treatment	53%	Asch ES J Rheumatology: 21: 454-461. (1994)
Late or chronic Lyme disease.	80%	Donta ST Clinic. Infectious Dis:25 S52-56 (1997)

This table suggests that early recognition and treatment is very important in preventing the long-term complications of Lyme disease. It also suggests that treatment according to the IDSA guidelines does not prevent complications in a small percentage of patients even in early stages of disseminated disease promptly treated.

As Dattwyler (2) has suggested, “there are several possible explanations for the presence of residual symptoms including continued infection, an immunologic process, permanent tissue damage resulting from the initial infection, and co-infection with another tick-borne pathogen”. There is therefore a real concern that IDSA guideline-based treatment may not eradicate the infection in every patient in all of the tissues, and that a pool of infecting organisms can remain even after four, six, or even twelve weeks of treatment in some patients.

Evidence of Ongoing Infection after Four, Six, and Twelve weeks of Treatment.

Several authors have stressed that there is a failure rate from initial antibiotic treatment at the level and duration recommended in the IDSA guidelines. Oksi (5)

assessed patients after antibiotic therapy for Lyme disease. 165 sero-positive patients diagnosed between 1990-1994 were followed after antibiotic treatment. Of the 165 patients, 136 were tested by polymerase chain reaction (PCR) testing. 14 of 136 patients (10%) were PCR positive after completion of antibiotic therapy. To prove ongoing infection, 3 of the patients who were PCR positive grew B. burgdorferi in cultured specimens. All 13 patients had been treated for at least 3 months with intravenous, and or oral antibiotics, the treatment producing only a temporary relief of symptoms. Nine patients were retreated with IV ceftriaxone for 4-6 weeks, and the response to treatment was considered good. The seriousness of persistent Lyme infection is illustrated by one patient in Oksi's study who had an MRI scan showing infarct-like lesions in the white matter two years after intravenous and oral therapy. To prove this lesion was due to ongoing Lyme infection, B. burgdorferi was cultured both from the blood and CSF of this patient, suggesting that 3 months of treatment had been inadequate in this case.

Waniek (6) reports a case of rapidly progressive dementia from Lyme disease. A 47-year-old patient was given what was thought to be an adequate course of antibiotic therapy over a 10 week period. The patient later presented with personality changes and a positive ELISA test. He was treated with 4 weeks of IV ceftriaxone followed by 6 weeks of oral antibiotics. Personality deterioration and dementia progressed and the patient eventually succumbed to aspiration pneumonia. Autopsy specimens of the CNS with silver staining showed spirochetes consistent with the Lyme spirochete, B. burgdorferi.

This case report, combined with Oksi's observation that 10% of cases remain PCR positive after three months of treatment, suggests some patients will have ongoing infection and will need further treatment.

Sigal (7), in reviewing 100 patients referred to a Lyme disease center in an endemic area, notes that the majority of patients did not have Lyme disease. Of the 100 patients, 37 were found to have Lyme disease. In this group most had received recommended antibiotic therapy, and serologic testing was done using IgG and IgM immunoblotting. 4 of the 37 patients (11%) were believed to have a recurrence of their Lyme disease.

This figure of a 10% treatment failure rate is similar to the figure reported by Oksi (5). There are other similarities between the two studies including the fact that both reports looked at patients who had previously been treated with what had been judged to be adequate antibiotic therapy.

Donta (8) in following 277 patients who had been treated with tetracycline therapy for periods ranging from one to 11 months (mean 4 months) reported that 20 % of patients were cured, 70% were improved, and treatment failed for 10% of patients. Donta states that lab. support for the diagnosis was made difficult because "ELISA tests have been unreliable; western immunoblotting has been more sensitive but more difficult to perform and standardize; and PCR analysis of DNA is insufficiently sensitive." He stresses that the patient's subjective reports of improvement are the most reliable measure of clinical outcome.

In his series, EIA tests were negative for 52% of patients, however 81% of patients had either a positive EIA or Western Blot test. Patients who had been previously treated with antibiotics had a lower rate of cure, 16% in the untreated and 31% in the previously treated group.

He believes that positive IgM reactions may represent reactivation of latent disease or persistent infection as has been noted in other chronic diseases (toxoplasmosis). The author stresses, however, that “seronegative Lyme disease is a recognized clinical entity, and our results demonstrate that patients with similar clinical symptoms who are seronegative have responses to antibiotic treatment that are not distinguishable from those of seropositive patients. These findings also suggest that circulating antibody responses are not the most relevant correlates of disease presence or activity. Until better diagnostic tests are available to document the presence and extent of infection, clinical criteria remain the mainstay of diagnosis.

The optimum treatment for chronic Lyme disease also remains to be delineated. No controlled trials have been conducted to date, yet there appear to be strong opinions regarding the type and duration of any antibiotic therapy ....although it has yet to be established whether all or most cases of chronic Lyme disease are due to persistent infection, our results support the hypothesis that it is a persistent infection and provide the basis for a reasonable approach to its management.” (8)

Donta also identifies a treatment failure rate of around 10% in his series. He suggests a longer treatment regimen than the IDSA guidelines of 4 to 8 weeks. “Our results show that a 3-6 month course of treatment is associated with cure or significant improvement in 80-90% of patients with chronic Lyme disease.” It is important to note, however, that his results show a 31% failure rate in patients previously treated with antibiotics.

Although there are several double-blind placebo-controlled studies available in patients with chronic Lyme disease, these studies follow the IDSA guidelines of brief antibiotic therapy and not unexpectedly fail to show improvement in patients with chronic Lyme disease. Donta makes the point that, “in patients with symptoms >1 year, the onset of any improvement frequently did not occur before 4-6 weeks of therapy had been given”. An example of this shortcoming is Kaplan’s retreatment study of cognitive function in 129 patients with neurologic symptoms after standard antibiotic therapy (10). He found no significant differences between the group treated with antibiotics for three months and those in the placebo group, as measured by standard tests of cognitive function. One might expect that patients who had previously been treated with antibiotics and failed, might, after three months, have some subjective improvement, but it would be too early to expect these results to show on standard psychological tests.

Donta (8) adds. “It would not then be surprising if both patients and physicians would conclude that this mode of therapy was ineffective when there was no improvement after 3-4 weeks of therapy. This slow rate of improvement may correlate best with organisms for which the rates of multiplication and metabolism are slow, as is known for B burgdorferi. We speculate that the frequently noted cycles of improvement and relapse can be consistent with the varying metabolic activities of a heterogeneous population of spirochetes.”

The Complex Microbiology of the Lyme Spirochete.

In addition to the slow metabolism of the Lyme spirochete as a cause of chronicity, Donta (8) notes the intracellular nature of the infection. “A third observation

was the hypothesis that chronic Lyme disease is a persistent intracellular infection. This hypothesis draws support from what is known about other chronic infections, of which most, if not all, have an intracellular reservoir (e.g. Chlamydia, Legionella, Leishmania, Rickettsia, and Mycobacterium tuberculosis). An intracellular location could also explain the difficulties posed for B-lactam antibiotics as a treatment of Lyme disease. This intracellular location is supported by data from a tissue culture model of B. burgdorferi infection in which ceftriaxone was ineffective against intracellular organisms (9). The possibility of intracellular infection may explain why patients can have negative cultures and negative PCR testing after 4 to 8 weeks of antibiotic therapy, and yet may still harbor a reservoir of infection hidden within the cells. It is this possibility that calls the following IDSA guideline statement into question:

" There is no convincing biologic evidence for the existence of symptomatic chronic B. burgdorferi infection among patients who receive recommended treatment regimens for Lyme disease." (1)

This is certainly one theory. Another theory, however, is that one would expect accessible joint and CSF fluids to be negative on culture and PCR testing after 4-6 weeks of antibiotics, but these negative tests do not exclude the possibility of an ongoing intracellular reservoir of dormant or inactive cells that can sooner or later become active and spread the infection. Because there is solid scientific evidence supporting this theory, it would appear that rigid treatment guidelines are inappropriate at this time.

Patients who have been infected for longer than one year may have a larger intracellular reservoir of infection and may require antibiotics for a much longer time to eradicate these organisms.

In discussing the treatment of tuberculosis and its relationship to cell metabolism, Avery (15) has the following comments:

"It is suggested that distinct populations of organisms exist in human infection, and their susceptibility to anti-tuberculosis drugs differ. Group-1 is rapidly growing and metabolically active. They respond to bactericidal doses of isoniazid, rifampin, and streptomycin. Group-2 has streaks of activity and respond best to rifampin. Group-3 organisms are within macrophages and respond best to pyrazinamide. Group-4 organisms are dormant, relatively unresponsive, and require prolonged therapy."

It is quite possible that this model also applies to Lyme disease where different phases of metabolic activity, both inside and outside cells, may be occurring. Avery points out that the therapy for uncomplicated tuberculosis with three antibiotics takes 6 months, with two antibiotics 9 months, and with one standard antibiotic combined with a second- line drug, 12 months.

If this model applies to Lyme disease, treatment for chronic infection may well need to extend over years rather than weeks or months. The complexity of treating the Lyme spirochete is illustrated in a paper by Brorson (11).

In his experiment a culture of B. burgdorferi was transferred after filtration, to a spinal fluid medium. Results showed that the spirochetes "converted rapidly to cystic forms when transferred to spinal fluid". Cysts were demonstrated and photographed using interference contrast microscopy. This finding suggests that cystic forms are likely present in CNS Lyme disease, a possible explanation for why standard monotherapy is not always successful. This study provides a theoretical basis for treating neurologic

Lyme disease with combination therapy, with at least one agent effective against the cystic form of the disease.

The Complexity of Evaluating Clinical Studies of Lyme Disease.

The complex issues raised in the evaluation of clinical studies of the treatment of Lyme disease are illustrated in Table 2.

TABLE - 2,
A SUMMARY OF SIX STUDIES OF TREATMENT OUTCOME IN LYME DISEASE.

STUDY-AUTHOR	MEASURE OF SUCCESS	DURATION OF THERAPY	OUTCOME
Oksi J. Ann Med: 31, 225-232 (1999)	PCR testing	3 months	10% of pts. still PCR positive
Klempner MS, NEJM:345 (2), 85-92 (200l)	Short Form General Health Survey	3 months (retreatment)	No improvement
Krupp LB, Neurology: 60 (12), 1923-30(2003)	Fatigue questionnaire and A-Arithmetic test	28 days (retreatment)	Improvement in fatigue. No improv. in cognitive funct.
Donta ST, Cl. Inf Dis: 25, Supplement, S52-6 (1997)	Absence of symptoms one year after therapy.	1-11 months (Median 3-6 months)	Retreated group 16% cured. Initial treatment group 31% cured.
Wormser GP, Ann Int Med: 138 (9),697-704 (2003)	Symptomatic improvement, plus psycho-neurologic test.	10-20 day doxycycline +/- single dose ceftriaxone. (early treatment)	84-90% cure
Kaplan RF Neurology:60 (12), 1916-1922 (2003)	Pain and cognitive tests, from Medical Outcome Study (MOS)	90 days. (retreatment study)	No difference between treatment and controls.

An inspection of Table-2 shows again that early treatment (as in the study by Wormser) produces a much higher probability of cure than later treatment (as in the study of Donta). In fact Donta's study demonstrates a cure rate of 31% in previously untreated patients as opposed to a cure rate of 16% in patients who have previously received antibiotic treatment (and are likely to be presenting at a later stage of their disease). There is obviously the potential for confusion in what constitutes successful treatment as each of the six authors has a different method of measuring successful treatment outcome.

There is, nevertheless, a clear indication that no matter which study one examines, there is a failure rate of treatment, and that failure rate appears to be between 10% and 84%, depending on the duration of the Lyme disease.

It appears that Dattwyler's statement (2) summarizes very nicely the present state of knowledge regarding the cause and treatment of residual symptoms in previously treated patients:

> "although there are several explanations for the presence of residual symptoms including continuing infection, an immunologic process, permanent tissue damage from the initial infection, co-infection with another tick-borne pathogen- the cause of post-treatment symptoms remains to be addressed in future studies".

Problems with the IDSA Guidelines:

There are certainly the aforementioned problems of the IDSA Guidelines in not recommending treatment for those bitten by the I.scapularis tick. Perhaps the most unscientific statement, however, is the denial of the existence of treatment failure and ongoing infection after treatment with antibiotics for the length of time recommended by the guidelines:

"There is no convincing biologic evidence for the existence of symptomatic B. burgdorferi infection among patients after receipt of recommended treatment regimens for Lyme disease. Antibiotic treatment has not proven to be useful and is not recommended for patients with chronic (>6 months) subjective symptoms after recommended treatment regimens for Lyme disease."(12)

Certainly the studies of Oksi and Donta (5,8) provide ample evidence of patients who have clinical evidence of ongoing infection after treatment and who show remission after retreatment. In Donta's study, which included many patients being retreated, the duration of therapy was as long as 11 months.. If further proof of the need for extended treatment is required, the autopsy result in the report of Waniek (6) provides absolute proof of the need for extended treatment in selected cases of Lyme disease.

It is my belief that the IDSA Guidelines are based on a narrow range of studies that take advanced and chronic cases and look for evidence of improvement as measured by very narrow parameters (such as neuropsychological tests) after only a few weeks of treatment. In fact in the studies that are quoted, if one reads them closely, there actually is evidence of some modest subjective improvement in as little as three months of therapy (13).

Conclusion:

In considering the unanswered questions regarding the microbiology of the Lyme spirochete, and the confusion among clinical studies, it appears premature and inappropriate for the IDSA to publish restrictive guidelines on the treatment of Lyme disease. There is definitely a well-documented rate of treatment failure in these short-term antibiotic regimens, and some supporting evidence for successful longer-term retreatment in selected patients.

It would be tragic if the IDSA guidelines (1), which for some patients are too time-limited and restrictive, were to exclude patients with early, intermediate, or late Lyme disease who might benefit from further antibiotic treatment.

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